

AD \_\_\_\_\_

AWARD NUMBER: W81XWH-13-1-0005

TITLE: Monitoring neurocognitive performance and electrophysiological activity after mild traumatic brain injury (mTBI)

PRINCIPAL INVESTIGATOR: Michael G. Harrington, M.B., Ch.B., F.R.C.P.

RECIPIENT: Huntington Medical Research Institutes  
Pasadena, CA 91105

REPORT DATE: March 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;  
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. <b>PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.</b>					
1. REPORT DATE March 2014		2. REPORT TYPE Annual		3. DATES COVERED 1 March 2013-28 February 2014	
4. TITLE AND SUBTITLE Monitoring neurocognitive performance and electrophysiological activity after mild traumatic brain injury (mTBI)				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-13-1-0005	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Michael G. Harrington, M.B., Warren Merrifield, PhD, Brian Ross, MD, PhD  Email: mghworks@hmri.org				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Huntington Medical Research Institutes 99 El Molino Street Pasadena, CA 91105				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The objective of the study is to develop of multimodal approach to assessing concussion in the acute phase of injury. Several different measures will be included in the assessment. These include functional brain measurement techniques, anatomical brain mapping techniques, biomarkers (blood protein levels), neurocognitive performance (computer-based tests), balance testing, and behavioral health measures. The ultimate aim is to develop an objective method to diagnose mTBI in military personnel proximal to the time of injury and facilitate 'return to duty' decisions.					
15. SUBJECT TERMS Traumatic Brain Injury, mTBI, concussion, Magnetoencephalography, MEG, MRI, biomarkers, actigraphy					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	7	19b. TELEPHONE NUMBER (include area code)

## Table of Contents

	<u>Page</u>
1. Introduction	4
2. Body	4
3. Keywords	4
4. Overall Project Summary	6
5. Key Research Accomplishments	6
6. Conclusion	6
7. Publications, Abstracts, and Presentations	6
8. Inventions, Patents and Licenses	6
9. Reportable Outcomes	6
10. Other Achievements	6
11. References	6
12. Appendices	7

## **1. INTRODUCTION**

The objective of the study is to develop of multimodal approach to assessing concussion in the acute phase of injury. Several different measures will be included in the assessment. These include functional brain measurement techniques, anatomical brain mapping techniques, biomarkers (blood protein levels), neurocognitive performance (computer-based tests), balance testing, and behavioral health measures. The ultimate aim is to develop an objective method to diagnose mTBI in military personnel proximal to the time of injury and facilitate ‘return to duty’ decisions.

## **2. BODY**

Prior to 6 JAN 2014, steps were taken to order equipment, prepare the facilities, and meet with senior staff at Huntington Memorial Hospital. In addition, Dr. Ross and team implemented and tested the new Diffusion Tensor Imaging (DTI) and Susceptibility-weighted Imaging (SWI) protocols with control participants and patients with TBI who fell outside of the range in the present protocol (e.g. age or other than mild TBI).

Since the beginning of preparations for the study began on a full-time effort on 6 JAN 2014, significant progress has been made with all four sections (i.e. Emergency Department, functional brain measurements, anatomical brain imaging, blood biomarkers) to prepare for the study. All technology has been tested and the process for recruitment has been established in the Huntington Memorial Hospital Emergency Department. Pilot testing has been conducted with functional brain measurements and anatomical brain imaging, which includes establishing the processing pipeline for analyses that will occur primarily at HMRI and those that will be analyzed with collaborators.

Today, 24 MAR 2014, marks the first full week of recruitment efforts with Huntington Memorial Hospital. It is expected that we will recruit approximately 5 to 7 patients per month, which would allow us to meet the expectations of the award within approximately two years of the writing of this report.

## **3. KEYWORDS**

Traumatic Brain Injury, mTBI, concussion, Magnetoencephalography, MEG, MRI, biomarkers, actigraphy.

## **4. OVERALL PROJECT SUMMARY**

Several objectives have been completed to prepare for the study in all four sections (i.e. Emergency Department, functional brain measurements, anatomical brain imaging, blood biomarkers). Each section is detailed below:

- a. Emergency Department Medicine (Robert Goldweber, MD)
  - i. Dr. Goldweber has successfully integrated the project by gaining support from senior leadership and staff ER physicians.

- ii. Dr. Goldweber, Ms. Shannon Thomas, and the HMRI team met with each member of the staff, discussing inclusion/exclusion criteria, and formulated the plan for recruitment both for controls and mTBI patients.
- b. Functional brain measurements, neurocognitive testing, sleep actigraphy (Warren Merrifield, PhD)
  - i. Magnetoencephalography (MEG) laboratory is fully operational after two weeks of cool down and testing in February 2014. Pilot testing of the MEG has shown performance consistent with prior operation resulting in several publications on an NIH-funded grant.
  - ii. The Electroencephalography (EEG) system has been tested and is fully operational. Dr. Merrifield attended training in San Diego on 7 FEB 2014.
  - iii. Neurocognitive testing device Defense Automated Neurobehavioral Assessment (DANA) has been acquired. James Drane from Anthornix provided cognitive assessments to include DANA Brief, DANA Brief Plus, and DANA Brief Standard. Pilot testing has been conducted by Dr. Merrifield in preparation for the study.
  - iv. Readiband actigraphy devices have been acquired, programmed, and tested.
- c. Anatomical brain imaging (Brian Ross, MD, PhD)
  - i. GE 1.5 Tesla superconducting MR upgraded system to a current 8-channel MR imaging system.
  - ii. DTI pulse sequences were added to the current MR system.
  - iii. Four different software tools are currently implemented and being tested. Following is each tool with preliminary observations.
    - 1. DTI-studio: adequate fractional anisotropy (FA) and apparent diffusion coefficient (ADC), poor tractography.
    - 2. Freesurfer: useful volumetric analysis; TRACULA.
    - 3. CAMINO: software will be used in collaboration with Dr. James Stone, University of Virginia.
    - 4. Dynasuite-Neuro: provides elegant tractography and co-registration tools, future fMRI, and perfusion mapping.
- d. Blood biomarkers (Michael G. Harrington, M.B., Ch.B., F.R.C.P)
  - i. Protocol for blood collection at MEG lab set up completed.
  - ii. Blood candidate protein sequences selected for stable isotope standards
  - iii. Options of mass spectrometers tested at Thermo Fisher Scientific for best performance with test peptides.
  - iv. Job description prepared for recruitment of analytical chemist.
- e. Study in patient with moderate TBI
  - i. Recently, Drs. Ross and Merrifield performed anatomical and functional imaging on a patient with TBI under another IRB-approved protocol with Dr. Ross as Principal Investigator and part of his clinical program. The patient had a clear coup-contrecoup injury, indicating moderate TBI, as determined by anatomical imaging. Additional measurements were

recorded by Dr. Merrifield using MEG. The data acquisition techniques and analysis procedures were identical to the currently approved protocol, which provided an additional trial run to the already successful pilot studies with control participants.

## **5. KEY RESEARCH ACCOMPLISHMENTS**

Nothing to report.

## **6. CONCLUSION**

The present study will provide the military and civilian research community with data pertaining to impact-related mechanisms of mTBI in the acute phase of injury. This information is important because blast-related trauma typically results in secondary (e.g., head being struck by flying debris) and tertiary (e.g., subject being propelled into a hard object) mechanisms of mTBI<sup>1</sup>. In addition, it has been estimated that 80% of all military mTBI occurs from events not related to combat or during deployment<sup>2</sup>. Our research will compliment other work done by investigators on this proposal using functional brain measurements (i.e. MEG, EEG) at the Walter Reed National Military Medical Center – National Intrepid Center of Excellence characterizing mTBI from blast and impact-related mechanism of injury and anatomical brain imaging examining repetitive blows from sports-related concussion<sup>3-7</sup>.

## **7. PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS**

Nothing to report.

## **8. INVENTIONS, PATENTS AND LICENSES**

Nothing to report.

## **9. REPORTABLE OUTCOMES**

Nothing to report.

## **10. OTHER ACHIEVEMENTS**

Nothing to report.

## **11. REFERENCES**

1. Warden D. Military TBI During the Iraq and Afghanistan Wars. *J Head Trauma Rehabil.* 2006; 21:398-402.
2. AFHSC. Deployment-Related Conditions of Special Surveillance Interest, U.S. Armed Forces, by Month and Service, January 2003-March 2013. Medical Surveillance Monthly Report (MSMR). <http://afhsc.army.mil/msmr>. Retrieved March 24, 2014.

3. Merrifield WS, Popescu M, Popescu A, Balbir A, Balkin TJ, Bleiberg J, Riedy G, DeGraba T. Localization of Delta Slow Wave Activity in Mild Traumatic Brain Injury (mTBI) using Independent Component Analysis. 2013. *Neurotrauma Conference*. Nashville, Tennessee.
4. Popescu M, Popescu A, DeGraba T, Balbir A, Bleiberg J, Riedy G, Balkin T, Merrifield W. Resting-State Brain Activity in mTBI Patients with High versus Low PTSD Symptom Severity. *National Capital Area TBI Research Symposium*. 2014. Bethesda, Maryland.
5. DeGraba M, Merrifield W, Mattingly E, Mikola J, Popescu M, Popescu A, Balbir A, Balkin T, Bleiberg J, DeGraba T. MEG Findings Correlate to Speech-Language Pathology Deficits in Combat-Related mTBI and PTSD. *American Academy of Neurology Conference*. 2014. Philadelphia, Pennsylvania.
6. Lin AP, Liao HJ, Merugumala SK, Stern RA, Ross BD. Regional Metabolite Profiles in Chronic Sports-Related Concussion. 10th World Congress on Brain Injury (2014) 10:831
7. Lin AP, Ramadan S, Stern RA, Box H, Nowinski C, Ross BD, Mountford CE. Changes in the Neurochemistry of Athletes with Repetitive Brain Trauma: Preliminary Results using Localized Correlated Spectroscopy. *Alzheimer Research and Therapy*. (In Press)

## 12. APPENDICES

Nothing to report.